

Pending Claims

Page 11 of 18

Serial No.: 10/027,277

Confirmation No.: 3061

Title: CRYSTALLIZATION AND STRUCTURE DETERMINATION OF GLYCOSYLATED HUMAN BETA
SECRETASE, AN ENZYME IMPLICATED IN ALZHEIMER'S DISEASE

Remarks

The Office Action mailed September 8, 2003 has been received and reviewed. Claims 2, 5, 18, and 23 having been amended, the pending claims are claims 1-25. Claims 19-25 having been withdrawn from consideration by the Examiner, claims 1-18 are currently under consideration.

The specification has been amended at page 18, line 20, and page 40, line 8, to clarify that Applicants are not intending to recite a hyperlink therein. The specification has also been amended at page 34, lines 14-15 to correct obvious typographical errors, the correction of which is supported by the specification at, for example, page 37, lines 15-16. The specification has been amended at page 42, line 9 and page 43, lines 1 and 2 to correct a typographical error to correctly recite the space group as P3₂21, as would be obvious to one of skill in the art. The specification has also been amended to correct typographical errors at page 38, lines 11, 12, and 25; page 39, line 30; page 41, line 11; and page 42, line 13, to correctly refer to Figure 1.

Claims 2, 5, and 23 have been amended to depend from claims 6, 13, and 21, respectively. Claims 2 and 5 have also been amended to recite the language "selected from the group consisting of." Claim 18 has been amended to recite "a" Baculovirus expression system.

Reconsideration and withdrawal of the rejections are respectfully requested.

Copending Application

Applicants directed the Examiner's attention to copending application Serial No. 10/028,224 in the Information Disclosure Statement mailed March 1, 2002. Applicants also wish to draw the Examiner's attention to the Office Action mailed August 12, 2003, and the rejections recited therein, for copending application Serial No. 10/028,224.

Provisional Statutory-Type Double Patenting Rejection

Claims 1-18 were provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 54-71 of co-pending Application Serial No. 10/028,224.

Upon an indication of otherwise allowable subject matter and in the event this rejection is maintained, Applicants will provide an appropriate response.

Provisional Obviousness-Type Double Patenting Rejection

Claims 1-18 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of co-pending Application Serial No. 10/144,441. Claims 1-5, 7-8, and 10-14 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-23 and 25-26 of co-pending Application Serial No. 10/143,723. Finally, claims 1-8 and 10-16 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-15 and 17-23 of co-pending Application Serial No. 10/143,502.

Upon an indication of otherwise allowable subject matter and in the event this rejection is maintained, Applicants will provide an appropriate response.

Objection to the Specification

The Examiner objected to the specification for allegedly containing embedded hyperlinks. The specification having been amended at page 18, line 20 and page 40, line 8, Applicants respectfully submit that the rejection has been rendered moot.

Applicants respectfully request that the Examiner reconsider and withdraw the objection to the specification.

Rejection under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 2, 5, 9, 16, and 17 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner rejected claims 2 and 5 for allegedly having insufficient antecedent basis. Claims 2 and 5 having been amended, Applicants respectfully submit that the rejection has been rendered moot.

The Examiner rejected claims 5, 9, 16, and 17 as allegedly being vague and indefinite for including abbreviations. Applicants respectfully submit that the abbreviations PEG, PEG-MME, PEG-DME, DMSO, CHO-K1, and HEK 293 are clear and definite to one of skill in the art. Further, the specification defines CHO, DMSO, and PEG at, for example, page 4, lines 6, 7, and 11, respectively, and PEG-MME and PEG-DME at, for example, page 6, lines 20-21.

Based on the amendments and remarks presented herein above, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §112, First Paragraph

Enablement

The Examiner rejected claims 1-18 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for lack of enablement in accordance with M.P.E.P. §2164.04. "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. . . . [The] examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure." (M.P.E.P. §2164.04). "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless

there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." M.P.E.P. §2164.04.

Present claims 1-18 are directed to a method for crystallizing a human beta secretase molecule or molecular complex. The specification describes crystallization methods (e.g., page 6, line 16 to page 7, line 9) and further, although not required, includes working examples (e.g., page 38, line 9 to page 39, line 20). Further, the Examiner acknowledged that "Applicants have disclosed information to enable one skilled in the art to make the trigonal space group P₃₂21 crystals of human beta secretase" (page 8, last paragraph of the Office Action mailed September 8, 2003). Thus, Applicants respectfully submit that the present claims are fully enabled by the specification.

However, the Examiner asserted that "the specification does not reasonably provide enablement for crystallizing other human beta secretase molecules or molecular complexes" (page 9, lines 2-3 of the Office Action mailed September 8, 2003), and that "[d]ue to the unpredictability and difficulty of crystallizing proteins, it is unlikely that one of skill in the art would be able to make another crystal relying solely on the information for the crystals disclosed in the specification without undue experimentation" (page 9, lines 10-13 of the Office Action mailed September 8, 2003). Applicants respectfully traverse the rejection.

Applicants respectfully submit that the Examiner has not provided a reasonable explanation as to why the present method claims are not adequately enabled by the disclosure. Notably, the Examiner has not provided any reason to doubt the objective truth of the disclosure provided in the specification. It is respectfully submitted that the Examiner's general statement regarding unpredictability of the art is not sufficient reason to doubt the truth or accuracy of Applicants' disclosed method of crystallizing human beta secretase, in accordance with the teachings of the specification.

Applicants also note that the Examiner asserted that "[t]he claim is broader than the enablement provided by the disclosure with regard to the large number of possible crystalline helicasases that could be made" (page 9, lines 4-5 of the Office Action mailed September 8, 2003).

Applicants respectfully note that none of the claims recite "crystalline *heliceses*." Applicants respectfully request clarification of the above assertion in the next Official Communication.

Written Description

The Examiner rejected claims 1-18 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the Examiner alleged that "[t]here is no disclosure regarding any crystals other than the trigonal space group P₃₂21 crystals of human beta secretase . . . As written, the claim may contain other crystals which do not meet the written description provision of 35 USC 112, first paragraph" (page 10 of the Office Action mailed September 8, 2003).

Applicants respectfully traverse the rejection. Claims 1-18 are directed to a method for crystallizing a human beta secretase molecule or molecular complex. Applicants respectfully submit that the description of crystallization methods in the specification (e.g., page 6, line 16 to page 7, line 9; page 38, line 9 to page 39, line 20), which includes working examples, is adequate to satisfy the written description requirement under 35 U.S.C. §112, first paragraph.

Moreover, the Examiner's remarks that there is "no disclosure regarding any crystals other than the trigonal space group P₃₂21 crystals," and that "the claim may contain other crystals" are not understood, as the claims presently under examination are directed to crystallization methods, not crystals *per se*. Applicants respectfully request clarification of the remarks in the next Official Communication.

Based on the remarks presented herein above, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §102

The Examiner rejected claims 1-3, 5-8, 10, and 13-14 under 35 U.S.C. §102(a) as being anticipated by Hong et al., *Science*, 290:150-153 (2000). The Examiner also rejected claims 1-3, 5-15, and 17 under 35 U.S.C. §102(e) as being anticipated by U.S. Pat. No. 6,545,127 (Tang et al.). Applicants respectfully traverse the rejections.

"[F]or anticipation under 35 U.S.C. 102, the reference must teach *every aspect* of the claimed invention either explicitly or impliedly." M.P.E.P. §706.02 (emphasis added). Independent claim 1 recites "crystallizing human beta secretase from a solution having a pH of about 3.5 to about 5.5."

In contrast, Hong et al. recite that "[p]urified recombinant memapsin-2 in the presence of fivefold molar excess of OM99-2 was crystallized in 0.2 M ammonium sulfate and 22.5% PEG 8000 buffered with 0.1 M Na-cacodylate (pH 7.4) at 20°C, using the hanging drop vapor diffusion method" (page 153, column 2, footnote 12).

Similarly, Tang et al. recite that "[c]rystals of memapsin-inhibitor complex were obtained at 30% PEG 8000, 0.1M NaCocadylate, pH 6.4" (column 31, lines 1-2), and that "[c]rystals of quality suitable for diffraction studies were obtained in two weeks in 0.1M sodium cacodylate, pH 7.4, 0.2M (NH₄)₂SO₄, and 22.5% PEG8000" (column 31, lines 39-41).

Applicants respectfully submit that, contrary to the Examiner's allegations (e.g., pages 11-12 of the Office Action mailed September 8, 2003), pH 7.4 (as disclosed by Hong et al.), and pH 6.4 and 7.4 (as disclosed by Tang et al.) are not pH about 3.5 to about 5.5 (e.g., independent claim 1).

Applicants respectfully submit that Hong et al. and Tang et al. fail to anticipate the present claims, and request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §102.

Request for Rejoinder

The claims currently under examination (i.e., claims 1-18) are directed to a method for crystallizing a human beta secretase molecule or molecular complex. Claims 19-23 are directed to crystals of beta secretase, and claims 24-25 are directed towards methods of producing human beta secretase. Applicants respectfully request reconsideration of the restrictions in this case and request that claims 19-25 be rejoined and examined concurrently with claims 1-18.

Information Disclosure Statement

The Examiner lined out citations to three electronic documents listed on 1449 forms submitted by Applicants, stating that they lacked publication dates on the actual copy. The documents are being resubmitted on a 1449 form with the Information Disclosure Statement submitted herewith. The 1449 form now lists publication dates for two of the documents. Applicants are not aware of a publication date for the document "BLAST 2 SEQUENCES," but hereby stipulate that the publication date is prior to December 23, 2000. Applicants respectfully request that the Examiner consider the above-cited documents.

Further, Applicants are attaching herewith a copy of a 1449 form (EXHIBIT A) submitted with an Information Disclosure Statement on September 3, 2003. Consideration of each of the documents listed on the attached 1449 form(s) is respectfully requested. Pursuant to the provisions of M.P.E.P. §609, Applicants further request that a copy of the 1449 form, marked as being considered and initialed by the Examiner, be returned with the next Official Communication.

Pending Claims

Page 18 of 18

Serial No.: 10/027,277

Confirmation No.: 3061

Title: **CRYSTALLIZATION AND STRUCTURE DETERMINATION OF GLYCOSYLATED HUMAN BETA SECRETASE, AN ENZYME IMPLICATED IN ALZHEIMER'S DISEASE**

Summary


It is respectfully submitted that all the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Benson et al.

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

March 8, 2004

Date

By: 
Loren D. Albin
Reg. No. 37,763
Direct Dial (612)305-1225

CERTIFICATE UNDER 37 CFR §1.10:

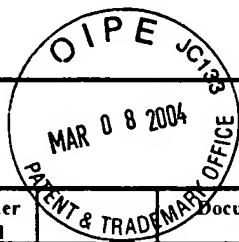
"Express Mail" mailing label number: **EV 073687885 US**

Date of Deposit: **MARCH 8, 2004**

The undersigned hereby certifies that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: 
Name: **SAM HER**

INFORMATION DISCLOSURE STATEMENT	Atty. Docket No.: 00481.CN1	Serial No.: 10/027,277
	Applicant(s): Benson et al.	Confirmation No.: 3061
	Application Filing Date: Dec. 21, 2001	Group: 1631
	Information Disclosure Statement mailed: SEPTEMBER 3, 2003	

**U.S. PATENT DOCUMENTS**

Examiner Initial	Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
	6,545,127 B1	04/08/03	Tang et al.			

FOREIGN PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Country	Class	Subclass	Translation	
						Yes	No
	NONE						

OTHER DOCUMENTS (Including Authors, Title, Date, Pertinent Papers, etc.)

Examiner Initial	Document Description
	Branden et al., "Introduction to protein structure," Garland Publishing, Inc., New York, NY 1999; Cover Page, Copyright Page, and pages 373-374.
	Bruinzeel et al., "Recombinant insect cell expression and purification of human β -secretase (BACE-1) for X-ray crystallography," <i>Protein Expr Purif.</i> 2002 Oct; 26(1):139-148.
	Ehehalt et al., "Splice variants of the β -site APP-cleaving enzyme BACE1 in human brain and pancreas," <i>Biochem Biophys Res Commun.</i> 2002 Apr 26;293(1): 30-37.
	Farzan et al., "BACE2, a β -secretase homolog, cleaves at the β site and within the amyloid- β region of the amyloid- β precursor protein," <i>Proc Natl Acad Sci U S A.</i> 2000 Aug 15;97(17):9712-9717.
	Ghosh et al., "Structure-based design: Potent inhibitors of human brain memapsin 2 (β -secretase)," <i>J Med Chem.</i> 2001 Aug 30;44(18):2865-2868.

EXAMINER	Date Considered
*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

EXHIBIT A